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Ethical Implications of Direct-to-Consumer Hereditary Cancer Tests

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Once limited to the clinical and research settings, direct-to-consumer (DTC) hereditary genetic tests are now available on the open market. Given the medical significance of these tests, there is a pressing need to address the unique ethical questions that arise when cancer susceptibility testing moves from the clinic to the DTC market. In this Viewpoint, we outline the current state of DTC genetic testing for hereditary cancer susceptibility, discuss ethical questions related to informed consent and the disclosure of consumers' test results, outline research needs, and recommend steps that DTC companies can take to promote informed consent and demonstrate the safe return of results.

Models of DTC Genetic Testing

The National Institutes of Health defines DTC genetic testing as the use of any genetic test that is marketed directly to consumers through a media outlet. Currently, there are 2 dominant models of DTC testing. The first model allows consumers to access a variety of health-related DTC genetic tests without a physician's order. With respect to hereditary cancer, the only test that is presently available through this model is a limited *BRCA* (*BRCA1* [OMIM113705], *BRCA2* [OMIM600188]) test (23andMe). The US Food and Drug Administration (FDA) authorized the company to test for 3 specific mutations that are most commonly seen in the Ashkenazi Jewish population. Recognizing that this *BRCA* test could pose a moderate to high risk of harm to users, the FDA's authorization included a set of regulatory criteria called special controls that, when met, provide reasonable assurance to the public that the test is safe and effective. In its press release, the FDA also acknowledged

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the limitations of the test and noted that the test is not recommended as a substitute for seeing a physician to better understand one's individual cancer risk.¹

The second model—physician-mediated DTC genetic testing—has been embraced by other companies (Color Genomics, Counsyl, Veritas Genetics).² Depending on the company's practices, consumers may be able to choose whether to have their own physician or a company-provided physician order their hereditary cancer test.

Pretest Counseling and Informed Consent

Direct-to-consumer genetic testing raises concerns about informed consent. As evidence of this worry, a recent study³ reported that 38% of participants did not consider the possibility of receiving unwanted information before purchasing DTC testing services. This concern is especially pronounced for panel testing. Because modern panels can include 25 to 50 different genes with varying degrees of penetrance and clinical utility, discussing the risks, benefits, and limitations associated with each gene being tested is impractical. Nevertheless, professional societies continue to recommend that patients receive pretest counseling and provide informed consent before undergoing cancer susceptibility testing, including with multigene panels.⁴

To address the challenge of ensuring informed consent to panel tests, new counseling models that organize information about multiple genes according to such variables as degree of penetrance and clinical action-ability have been proposed. Given differences in companies' pretest practices, it is unclear how well this approach translates to DTC genetic testing because consumers may not complete the informed consent process until after they have already requested, purchased, and received a test kit. Inasmuch as DTC companies' practices often diverge from professional recommendations and clinical practice, research should explore the extent to which consumers appreciate the risks, benefits, and limitations of DTC hereditary cancer susceptibility tests before they purchase a test kit.

Potential Concerns After Disclosure of Results

Direct-to-consumer hereditary cancer panels also raise questions about the safe return of results. Thus far, researchers have not found evidence of significant health-related behavioral changes among individuals receiving elevated cancer risk estimates through DTC testing.^{5,6} Most of the data, however, come from studies that used single-nucleotide variation profiling to determine participants' risk estimates, which has low predictive value and clinical utility.

For DTC testing that involves higher-penetrance genes, outcome data are limited. Although one published study⁷ found no evidence of adverse emotional or behavioral outcomes among consumers who underwent a *BRCA1/2* test, this was a small study in a select population and testing was limited to the 3 *BRCA1/2* mutations that are prevalent in the Ashkenazi Jewish population. Given these limitations, more research is needed to determine whether consumers react differently when their risk estimates are based on high- and moderate-penetrance mutations in cancer-susceptibility genes. In particular, research should explore how consumers respond to DTC panel tests, which may yield uncertain results (eg, variants of uncertain significance or unclear risk estimates).

Determining whether there are harms associated with the return of results will involve studying consumers' responses to different types of results. In particular, research should investigate whether consumers who receive a positive result share their findings with a medical professional and, if indicated, follow clinical recommendations for risk reduction. Another important question is whether individuals who receive a variant of uncertain significance finding wrongly seek increased surveillance or adopt inappropriate health-related behaviors.

Another possible risk of DTC hereditary cancer tests is psychological harm. Of particular concern is the possibility that consumers who receive a positive result through DTC testing will experience greater distress than patients who receive a positive result in the clinical setting. Although there is little evidence that patients who receive a positive *BRCA1/2* test result in the clinical setting experience long-term psychological distress, the extent to which this pattern is attributable to careful genetic counseling remains unsettled. Research should, therefore, investigate whether individuals who receive similar results through DTC testing exhibit comparable outcomes.

Finally, research should seek to understand whether there are differences between the consumer population pursuing DTC testing and the patient population undergoing clinic-based testing (ie, demographics, personal and/or family history of cancer, and motivation for testing) that might affect outcomes. It is possible that the DTC population is well suited to receive their results outside the clinical setting, perhaps because they are highly informed and can understand the complexities of results. If that is the case, the availability of DTC cancer tests may ultimately benefit consumers by democratizing access to genetic information.

Conclusions

Given the inherent complexity of multigene panels and the potential influence that testing could have on consumers, we suggest that DTC companies that offer hereditary cancer panels be required to take steps to promote informed consent and demonstrate the safe return of results. First, consumers should undergo the informed consent process before purchasing a test kit rather than after the kit has already been paid for and received in the mail. Second, companies should clearly communicate, as part of the informed consent process, the range of cancer spectra, risk estimates, and medical management options associated with the genes being tested. Third, companies should provide data demonstrating favorable behavioral and psychological outcomes for consumers receiving positive, negative, and variant of uncertain significance results. These data should address the spectrum of genes that comprise larger panels, including genes with limited clinical utility.

Beyond improved company practices, we anticipate that health care professionals will play an increasingly important role in promoting consumer safety. Health care professionals will need to be prepared to address patients' posttest concerns and consider referral to a genetics specialist if they lack the expertise to answer questions and provide medical management recommendations. As more consumers pursue DTC testing for hereditary cancer risk, we

hope that evidence-based policies will ensure the responsible provision of tests and the safe return of results.

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